

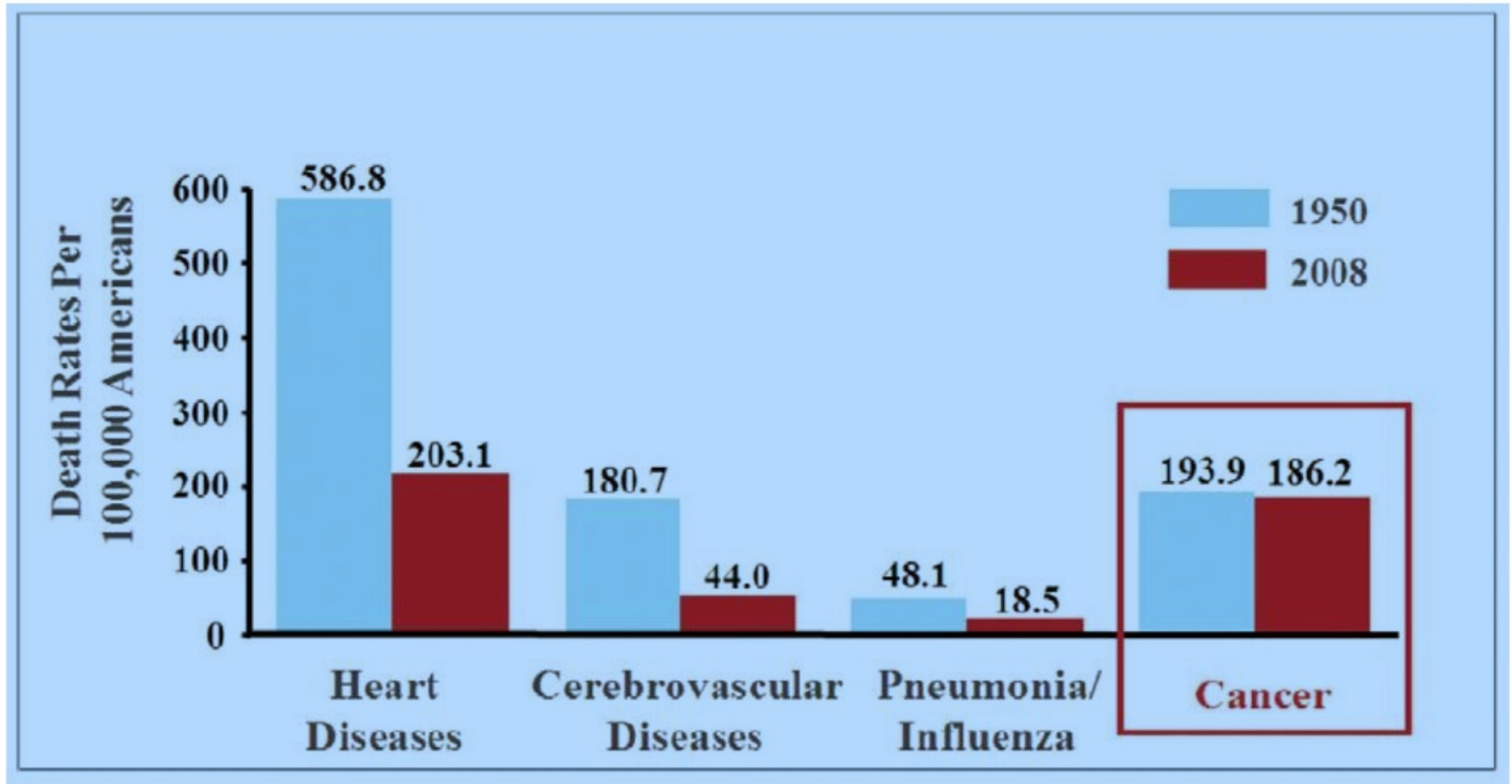
# **Preface: Some Data on Cancer**

*Giuseppe Longo*

Centre Cavallès, CNRS et Ecole Norm. Sup., Paris  
and Biology Depart., Tufts Univ., Boston  
[www.di.ens.fr/users/longo](http://www.di.ens.fr/users/longo)

*Collaboration with C. Sonnenschein, A. Soto, cancer biologists, Boston*

# Some Data on Cancer (USA)



While almost doubling the therapeutical success,  
thus doubling incidence

# Some Data on Cancer

- **endocrine target organs**, cancer general increase (1994 – 2012) :  
*breast 26% ; testis 56% ; prostate 94%*
- **thyroid cancer** ( +285% in 30 years, till 2012)

S. De Coster, N. van Larebeke, Endocrine-disrupting chemicals, **J. Environ. Public Health** 2012.

N. Howlander, et al, SEER Cancer Statistics Review, 1975–2012,  
**National Cancer Institute.**

# Some Data on Cancer

- **endocrine target organs**, cancer general increase (1994 – 2012) :  
*breast* 26% ; *testis* 56% ; *prostate* 94%
- **thyroid cancer** ( +285% in 30 years, till 2012)

S. De Coster, N. van Larebeke, Endocrine-disrupting chemicals, **J. Environ. Public Health** 2012.

N. Howlander, et al, SEER Cancer Statistics Review, 1975–2012,  
**National Cancer Institute.**

- **lowering by 50% (!) of human spermatozoa density** in the last 60 years

E. Diamanti-Kandarakis et al. *Endocrine-disrupting chemicals: an **Endocrine Society scientific statement***. **Endocr Rev** 30:293-342, 2009 % %

See also:

[http://www.dailymotion.com/playlist/xrczr\\_oversken\\_males-en-peril/](http://www.dailymotion.com/playlist/xrczr_oversken_males-en-peril/)

# “Doses” of Chemicals in the Ecosystem

*Unnoticed Endocrine Disruptor*, among:

**82,000** artificial molecules produced in the XX century

**(FDA, Fed. Drug Adm. Report to Congress, 2008)**

*A famous example: BPA as carcinogen*, 2 mln tons/year, in the ‘90s:

Soto, A.M., Justicia, H., Wray, J.W., Sonnenschein, C., **1991**

A. Soto, C. Sonnenschein. *Environmental causes of cancer: endocrine disruptors as carcinogens*. **Nat Rev Endocrinol.** 6:363-370, **2010**

*Till then: Do not worry: small doses and not stereo-specific*

# “Doses” of Chemicals in the Ecosystem

***Unnoticed Endocrine Disruptor***, among:

**82,000** artificial molecules produced in the XX century

**(FDA, Fed. Drug Adm. Report to Congress, 2008)**

*A famous example:* **BPA as carcinogen**, 2 mln tons/year, in the ‘90s:

Soto, A.M., Justicia, H., Wray, J.W., Sonnenschein, C., **1991**

A. Soto, C. Sonnenschein. *Environmental causes of cancer: endocrine disruptors as carcinogens*. **Nat Rev Endocrinol**. 6:363-370, **2010**

*Till then:* Do not worry: **small doses and not stereo-specific**

***False:***

- **low** chemical affinities, **non-linear** effects
- **varying** association/dissociation constants, **contextual**
- macromolecular interaction must be given in **probabilities**, and these depend on the **context** (since the ‘50s in physico-chemistry)

# The information-computational views: Stereo-specificity and the Central Dogma

1 - Exact macro-molecular (chemical and stereo) correspondence :

« The cell is ... a Cartesian Mechanism autonomous, **exact**,  
**independent** from external influences ...

**Necessarily stereospecific** molecular interactions explain the  
structure of the code ... a boolean algebra, **like in computers** »

[Monod, 1970]

The **key-lock** paradigm, in particular for cells' (hormons') receptors

# The information-computational views: Stereo-specificity and the Central Dogma

1 - Exact macro-molecular (chemical and stereo) correspondence :

« The cell is ... a Cartesian Mechanism autonomous, **exact**, **independent** from external influences ...

**Necessarily stereospecific** molecular interactions explain the structure of the code ... a boolean algebra, **like in computers** »

[Monod, 1970]

The **key-lock** paradigm, in particular for cells' (hormons') receptors

2 - Central Dogma (of molecular biology): *unidirectional information*:

**“DNA makes RNA and RNA makes proteins”** [Crick, 1958]

DNA: the **complete** *information* (set of *instructions*) for ontogenesis

The case of cancer ... %



# The DNA, the locus of **Discrete (Digital) Information** + **Central Dogma implied :**

Any phenotype has an antecedent in the genotype

More: The genotype is a "complete determination" of the phenotype

Once decoded the DNA we will be able to transfer it on a CD-rom  
and say: “**Here is a human being, this is me**”

(Gilbert, 1992)

“Selection targets **only genetic information**, organisms are **mere vehicles** .. avatars”  
(Gouyon et al., 2002; pp. 154-5)

# The DNA, the locus of **Discrete (Digital) Information** + **Central Dogma implied :**

Any phenotype has an antecedent in the genotype

*More:* The genotype is a "complete determination" of the phenotype

Once decoded the DNA we will be able to transfer it on a CD-rom  
and say: “**Here is a human being, this is me**”

(Gilbert, 1992)

“Selection targets **only genetic information**, organisms are **mere vehicles** .. avatars”  
(Gouyon et al., 2002; pp. 154-5)

- The *gene of marital fidelity* (Young et al., **Nature**, 400, 766-788, 1999)
- The *gene of longevity* (Migliaccio et al., **Nature**, 402, 309-313, Nov. 1999)
- The gene of **obesity** (N.Y. Rockefeller Center, 2000)
- ... the search for the “(proto-)**oncogene**”, “**onco-suppressor gene**” ...

Robert A. Weinberg, *MIT Center for Molecular Oncology*, major promotor of the **genocentric approach to cancer**

Co-author of a "classic" synthesis, **2000**, year of DNA decoding:  
Hanahan D and Weinberg RA. *The hallmarks of cancer*. **Cell**,  
100, 57–70, **2000**. (**20,000 citations** by 2010; 4,000, *pre-print*)

« ... **cancer biology and treatment ... will become a science** with a conceptual structure and logical coherence that rivals that of chemistry or physics », promising ... *dia-prognosi*, “magic bullet” ...

Robert A. Weinberg, *MIT Center for Molecular Oncology*, major promotor of the **genocentric approach to cancer**

Co-author of a "classic" synthesis, **2000**, year of DNA decoding:  
Hanahan D and Weinberg RA. *The hallmarks of cancer*. **Cell**,  
100, 57–70, **2000**. (**20,000 citations** by 2010; 4,000, pre-print)

« ... **cancer biology and treatment ... will become a science** with a conceptual structure and logical coherence that rivals that of chemistry or physics », promising ... dia-prognosi, “magic bullet” ...

Weinberg RA, *Coming Full Circle – from endless complexity to simplicity and back again*, **Cell** 157, March 27, **2014** (tough autocritique:  
« **one should never, ever confuse cancer research with science** »)  
(150 citations)

Longo G. *The Biological Consequences of the Computational World: Mathematical Reflections on Cancer Biology*, **in print**, 2017.

# Conclusion on Cancer

Easy therapeutical **myths** of SMT:

**re-program** the de-programmed cell (Nixon 1971, Collins 2000 ...):

*Even after the genome decoding (Venter, Weinberg)?*

“There comes a time when the mind's preference is for what confirms its knowledge rather than what contradicts it, for answers rather than questions. The conservative instinct then dominates and intellectual growth stops”. (Bachelard, 2002, p. 25)

It is difficult to get a man to understand something, when his salary depends upon his **not** understanding it.

—Upton Sinclair, author

# Genetically Modified Organisms

**GMO's: the direct heritage of the *Central Dogma***

DNA: the *complete information* (set of *instructions*) for ontogenesis

“drive the plant from the DNA”

# GMO's: the direct heritage of the *Central Dogma*

Remember: the **completeness of the DNA coding** of an organism  
« the organism: a mere vehicle ... », « once the DNA fully decoded  
... on a CD-rom... this is a man, this is me » [many authors]

Besides indirect consequences of **pesticides resistance** (absorption, transfer ...), thus more ***endocrine disruptors***, also:

# GMO's: the direct heritage of the *Central Dogma*

Remember: the **completeness of the DNA coding** of an organism  
« the organism: a mere vehicle ... », « once the DNA fully decoded  
... on a CD-rom... this is a man, this is me » [many authors]

Besides indirect consequences of **pesticides resistance** (absorption, transfer ...), thus more ***endocrine disruptors***, also:

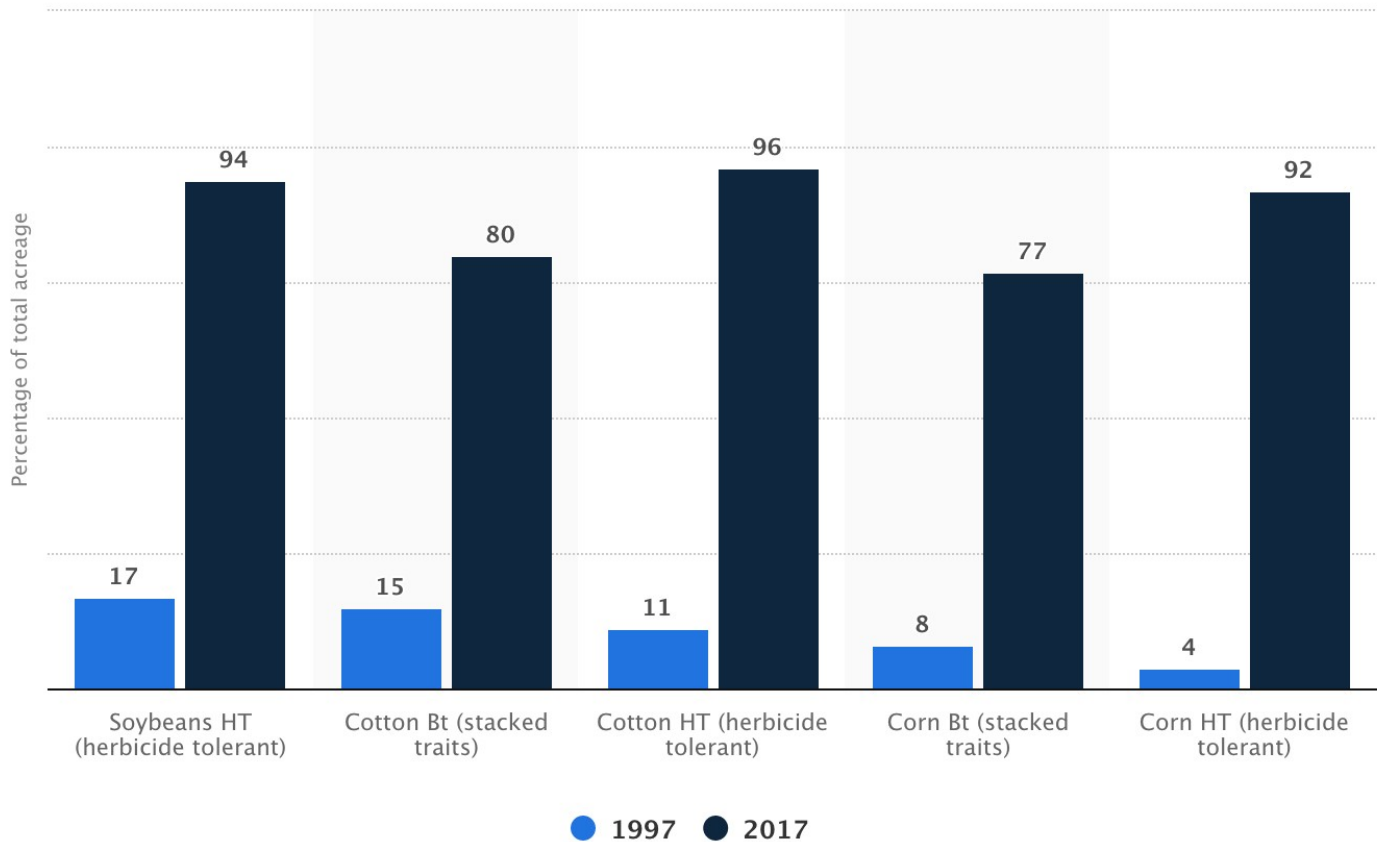
*Major modifications of microbial flora and fauna* (fungi, roots, soil)

- G.A. Kowalchuk et al., 2003. Assessing responses of soil microorganisms to GM plants. **Trends in Ecology and Evolution** 18, 403–410.
- M. Castaldini, et al, 2005, Impact of Bt Corn on Rhizospheric and Soil Eubacterial Communities and on Beneficial Mycorrhizal Symbiosis in Experimental Microcosms, **Applied and environmental Microbiology**, 71: 6719-29
- M. A. Badri et al., 2009, Unintended molecular interactions in transgenic plants expressing clinically useful proteins..., **Proteomics**, 9: 746–756.



# GMO's: the direct heritage of the *Central Dogma*

Percentage of genetically modified crops in the U.S. in 1997 and 2017, percent of total acreage)



DOWNLOAD

SETTING

PNG + PDF

DESCRIPTION

SOURCE

This statistic shows the genetically modified in t 2017, by type, as a perc each crop. In 2017, som crops were herbicide to

## Some references

- Soto, A. M. & Sonnenschein, C. *Environmental causes of cancer: endocrine disruptors as carcinogens*. **Nat. Rev. Endocrinol.** 6, 363–370 (2010).
- Cohn, B. A. et al. *DDT exposure in utero and breast cancer*. **J. Clin. Endocrinol. Metab.**, 2015 [http:// dx.doi.org/10.1210](http://dx.doi.org/10.1210)
- National Cancer Institute. **SEER cancer statistics factsheets: breast cancer** [online], <http://seer.cancer.gov/statfacts/html/breast.html> (2015).
- Paulose, T., Speroni, L., Sonnenschein, C. & Soto, A. M. *Estrogens in the wrong place at the wrong time: fetal BPA exposure and mammary cancer*. **Reprod. Toxicol.** 54, 58–65 (2015)
- Skakkebaek N., *Sperm counts, testicular cancers, and the environment*. **BMJ**, October 10, 2017
- Longo G. The Biological Consequences of the Computational World: Mathematical Reflections on Cancer Biology, **submitted**, 2017.

# **Les mathématiques entre normativité et imagination Historicité, finance et sémiogenèse**

*Nous sommes un groupe de mathématiciens qui dénonçons une mathématisation du monde orientée vers le contrôle, le quantitatif et le réductionnisme ....*

Giuseppe Longo (CNRS, ENS, « La difficile friction entre mathématiques et sciences historiques, à partir de la biologie »

Nicolas Bouleau (Ecole des Ponts ParisTech), « Finance : peut-on mettre l'interprétation en marché ? »

Alessandro Sarti (CNRS, EHESS), « L'intelligence entre élaboration de l'information et production de sens »

**14 décembre 2017, 14h, ENS, Paris, 45 rue d'Ulm, Salle Dussane**  
Lancement de l'association "Girolamo Cardano"